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Executive Director

Letter of support for Minimal Disease Activity Score (MDA) as primary outcome instrument for clinical studies in psoriatic arthritis (PsA)

Procedure

On 09/01/2021 the Applicant Team-It Research S.L. requested scientific advice for the use of the Minimal Disease Activity (MDA) score and the Psoriatic Arthritis Disease Activity (PASDAS) score as potential primary outcome instruments for clinical trials in psoriatic arthritis (PsA).

During its meeting held on 28 October 2021, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 11 November 2021, the CHMP adopted the advice to be given to the Applicant. The CHMP considered that the uncertainties associated with the PASDAS do not allow a positive conclusion with respect to a letter of support or Qualification Opinion. For the MDA criteria, the CHMP agreed to provide a letter of support.

The response given by the CHMP was based on the questions and supporting documentation submitted by the Applicant, considered in the light of the current state of the art in the relevant scientific fields.

Background and rationale for the proposed Minimal Disease Activity (MDA) score in drug development

Psoriasis is a chronic skin condition affecting about 3% of Europeans and North Americans. About 15% of people afflicted with psoriasis will develop psoriatic arthritis (PsA), a complex chronic heterogeneous inflammatory disease characterized by several different clinical manifestations. Historically, clinical subgroups have been described, simplified to axial and peripheral joint involvement, the latter dividing into oligo- and polyarticular patterns. However, important additional clinical PsA features are enthesitis (inflammation at the insertion of ligaments and tendons), dactylitis (uniform inflammation throughout a digit) and the skin and nails disease. These clinical subdivisions or “domains” of disease can combine in different patterns within each individual affected, reflecting the heterogeneity in all manifestations of this disease, including response to treatments.

In the biologic treatment era, and with renewed interest in psoriatic arthritis, research into outcome assessment has facilitated a clearer understanding of how these new drugs work on the different aspects of the disease.

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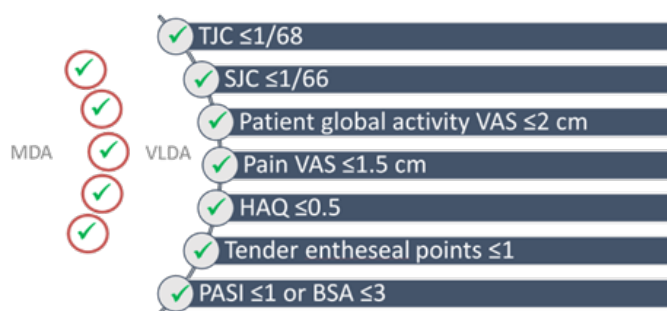
Due to PsA composite clinical features, the key to optimal treatment is to consider all aspects of the disease. This approach has been acknowledged and ratified by the Outcome Measurement in Rheumatology Clinical Trials (OMERACT) group, which has collaborated with the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).¹

International treatment recommendations were published by the GRAPPA in 2009, 2015 and further updated in 2021, based on a full literature review and expert consensus.² They outline the different treatments that are considered efficacious for six main domains of PsA. The ideal drug to treat this condition is one which is efficacious against all aspects of the disease, and thus, all aspects of the disease should be evaluated in clinical trials.

Remission is the ultimate goal of treatment in PsA and should be characterised by “a complete absence of disease activity, with no signs or symptoms of active disease”. However, remission is difficult to achieve and maintain, and “near remission” or “low disease activity” can be a desirable goal for treatment in individual patients.³

The European Medicines Agency (EMA) published a guideline in 2006 specifically related to the evaluation of medicinal products to treat PsA⁴ and currently endorses the American College of Rheumatology response criteria (ACR20), which was developed for use in Rheumatoid arthritis (RA) clinical trials. Whilst PsA is essentially an inflammatory arthritis, and the ACR response criteria do reflect improvement in PsA, these criteria focus specifically only on one domain of PsA disease, namely peripheral arthritis, and do not specifically reflect disease activity in enthesitis, dactylitis, axial or skin disease, which significantly affect patients' quality of life. Composite outcome measures developed specifically for PsA could more accurately reflect the clinical manifestations of this complex heterogeneous disorder, also simplifying the consideration of treatments as efficacious.

The Minimal Disease Activity (MDA) score was developed specifically to provide a disease activity target in psoriatic arthritis. This measure was designed using data from patients with PsA and was developed using current psychometric techniques.^{3,5,6} It defines the state of disease activity deemed a useful target of treatment by both the patient and physician, also considering the current treatment possibilities and limitations. The MDA criteria have been validated in several patient databases and cases of both high and low disease PsA activity, incorporating measures of all the important aspect of the PsA disease, as recommended by OMERACT.^{3,7-9} MDA is a binary variable that characterises a state that is close to remission, with possible residual disease; as “minimal disease activity” (MDA) is assigned if 5 of the following 7 criteria are met. If all criteria are met, the state is defined as “very low disease activity” (VLDA). The Peripheral joint activity is measured using the tender joint count (TJC, 0-68) and the swollen joint count (SJC, 0-66). Skin activity is represented by the Psoriasis Activity and Severity Index (PASI, 0-72) score or by the body surface area (BSA, 0-100) in the case of patients with low psoriasis disease activity. Pain and patient's global assessment of disease activity are measured using 100 mm visual analogue scales (VAS, 0-100), and the health assessment questionnaire (HAQ, 0-3) is used as a measure of physical function. A raw enthesitis count is included with a maximum value of 13, the maximum score of the commonly used measures in PsA.³



Dactylitis is captured by the peripheral joint count, where the dactylitic digits result in a quantifiable tender and/or swollen joint count. The spinal disease is identified by the patient's assessment of pain, global disease activity, and physical function and there are currently no available established outcome measures that are specific of spinal disease activity in this condition. Thus, MDA does not include specific measurements of axial disease activity. Further details can be found in the references listed.^{3,7-9}

The proposed Context-of-Use

The state of PsA disease activity in adult patients can be defined by the MDA criteria and is intended to be used in interventional or observational studies.

Proposed use in clinical studies:

- Phase III/IV trials (showing significant clinical benefit) rather than phase II trials (looking for initial signal of efficacy).
- Novel PsA therapeutic strategies could benefit from utilising the MDA measure as primary outcome for the evaluation of their efficacy, particularly in comparison with treatments currently in use.
- MDA would be beneficial in post-marketing studies investigating real-world effectiveness of therapy in wider populations as well as in longitudinal observational studies including registries. MDA could also be used in strategy trials either as a treatment target guiding drug escalation or as a primary endpoint.

Summary of the qualification advice

The EMA supports the strength of the proposed MDA definition, considering it as a desirable treatment target in PsA based on physician and patient concordance, acknowledging the stringency of its thresholds at patient's level, and the potential use as a primary endpoint in drug development despite the arbitrary element in the cut off selection.

It is agreed that the MDA, as a composite score, may disregard improvements in some components and deterioration in others. This is not a specific MDA gap but an inherent problem of composite scores. Indeed, this gap can only be evaluated by assessing at the same time the individual components of the composite, which should be included as secondary outcomes in clinical trials and their distribution should always be evaluated to facilitate interpretation.

The Applicant would need to comprehensively present evidence supporting that this outcome measure has reliability and that its sensitivity to change to pick up a treatment effect has been demonstrated in a clinical trial setting and in fact uniformly/adequately across the PsA severity/phenotype spectrum. Furthermore, it should be shown that a "minimal disease activity" is also perceived as such by the patient and perceived as such regardless of which of the 5 criteria are met. In relation to that, it should

be shown that the potential for and amount of misclassification (patients who would not be regarded as having MDA by external criteria but are classified as such by the instrument) is sufficiently low.

Although EMA recognises that MDA has been used in interventional and observational studies in PsA, the performance of MDA as an endpoint in a prospective randomised interventional study is considered as a pending final validation step.

References

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